

10/760672

FILE 'REGISTRY' ENTERED AT 14:24:10 ON 17 MAR 2006
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STRUCTURE FILE UPDATES: 15 MAR 2006 HIGHEST RN 877033-93-7
DICTIONARY FILE UPDATES: 15 MAR 2006 HIGHEST RN 877033-93-7

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH January 6, 2006

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conducting SmartSELECT searches.

*
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added, *
* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *
*

Structure search iteration limits have been increased. See HELP SLIMITS
for details.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document. For information
on property searching in REGISTRY, refer to:

<http://www.cas.org/ONLINE/UG/regprops.html>

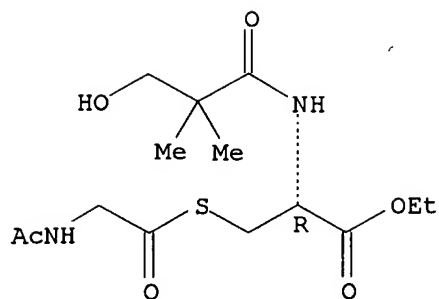
L1 E SPM 4757/CN *selected*
2 S E6-7
L2 E "SP/W 4757"/CN 5
L3 2 S E1 OR E6 *Compound*
4 S L1 OR L2 *what?* *- key terms*

L3 ANSWER 1 OF 4 REGISTRY COPYRIGHT 2006 ACS on STN
RN 316365-71-6 REGISTRY
ED Entered STN: 24 Jan 2001
CN L-Cysteine, N-(3-hydroxy-2,2-dimethyl-1-oxopropyl)-, ethyl ester,
3-[(acetylamino)acetate] (9CI) (CA INDEX NAME)

OTHER NAMES:
CN SP/W 6373
FS STEREOSEARCH
MF C14 H24 N2 O6 S
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

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PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

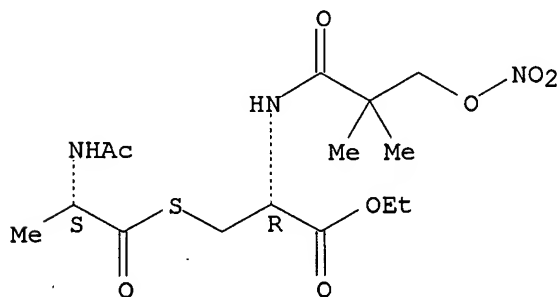
2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 2 OF 4 REGISTRY COPYRIGHT 2006 ACS on STN
RN 139146-66-0 REGISTRY
ED Entered STN: 21 Feb 1992
CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester,
ester with N-acetyl-L-alanine (9CI) (CA INDEX NAME)

OTHER NAMES:

CN **SPM 5185**
FS STEREOSEARCH
MF C15 H25 N3 O8 S
SR CA
LC STN Files: ADISINSIGHT, ADISNEWS, CA, CAPLUS, IMSDRUGNEWS,
IMSRESEARCH, MEDLINE, PROUSDDR, TOXCENTER, USPATFULL

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

21 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
21 REFERENCES IN FILE CAPLUS (1907 TO DATE)

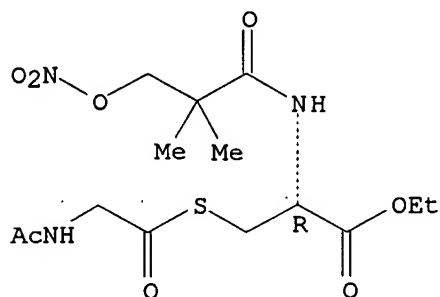
L3 ANSWER 3 OF 4 REGISTRY COPYRIGHT 2006 ACS on STN
RN 139146-65-9 REGISTRY
ED Entered STN: 21 Feb 1992
CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester,
ester with N-acetylglycine (9CI) (CA INDEX NAME)
OTHER NAMES:

Searcher : Shears 571-272-2528

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CN SP/W 5186
CN **SPM 5186**
FS STEREOSEARCH
MF C14 H23 N3 O8 S
SR CA
LC STN Files: ADISINSIGHT, BIOSIS, CA, CAPLUS, CIN, PHAR, PROUSDDR,
TOXCENTER, USPATFULL

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

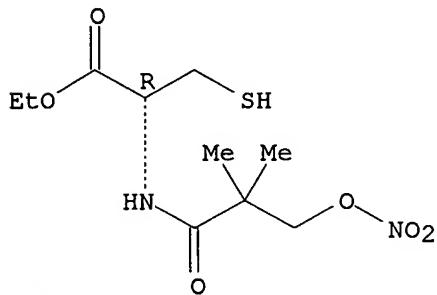
8 REFERENCES IN FILE CA (1907 TO DATE)
8 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 4 OF 4 REGISTRY COPYRIGHT 2006 ACS on STN
RN 130432-17-6 REGISTRY
ED ~~Entered STN~~ 16 Nov 1990
CN L-Cysteine, N-[2,2-dimethyl-3-(nitrooxy)-1-oxopropyl]-, ethyl ester
(9CI) (CA INDEX NAME)

OTHER NAMES:

CN **SP/W 3672**
CN SPM 3672
FS STEREOSEARCH
MF C10 H18 N2 O6 S
SR CA
LC STN Files: BIOSIS, CA, CAPLUS, EMBASE, IMSRESEARCH, MEDLINE,
PROUSDDR, TOXCENTER, USPATFULL

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

Searcher : Shears 571-272-2528

10/760672

20 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
20 REFERENCES IN FILE CAPLUS (1907 TO DATE)

FILE 'CAPLUS' ENTERED AT 14:24:11 ON 17 MAR 2006
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FILE COVERS 1907 - 17 Mar 2006 VOL 144 ISS 13
FILE LAST UPDATED: 16 Mar 2006 (20060316/ED)

Effective October 17, 2005, revised CAS Information Use Policies apply. They are available for your review at:

<http://www.cas.org/infopolicy.html>

L1 2 SEA FILE=REGISTRY ABB=ON PLU=ON ("SPM 5185"/CN OR "SPM 5186"/CN)
L2 2 SEA FILE=REGISTRY ABB=ON PLU=ON "SP/W 3672"/CN OR "SP/W 6373"/CN
L3 4 SEA FILE=REGISTRY ABB=ON PLU=ON L1 OR L2
L4 39 SEA FILE=CAPLUS ABB=ON PLU=ON L3 OR SPM4757 OR SPM5186 OR SPM5185 OR SPM3672 OR SPM6373 OR SPW4757 OR SPW5186 OR SPW3672 OR SPW6373 OR (SPM OR SP(W)W OR SPW) (W) (4757 OR 5186 OR 5185 OR 3672 OR 6373)
L5 3 SEA FILE=CAPLUS ABB=ON PLU=ON L4 AND (GASTROINTESTIN? OR ULCER? OR GASTR? INTESTIN?)

L5 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2006 ACS on STN
ED Entered STN: 21 Feb 2003

ACCESSION NUMBER: 2003:132965 CAPLUS

DOCUMENT NUMBER: 138:163603

TITLE: Methods for novel sulfur-containing organic nitrate compounds use in the treatment and prevention of human diseases and conditions

INVENTOR(S): Garvey, David S.; Letts, L. Gordon

PATENT ASSIGNEE(S): Nitromed, Inc., USA

SOURCE: PCT Int. Appl., 43 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003013432	A2	20030220	WO 2002-US24923	20020807

Searcher : Shears 571-272-2528

APP

10/760672

WO 2003013432 A3 20031113
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH,
CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD,
GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ,
LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ,
NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ,
TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ,
BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
CA 2453433 AA 20030220 CA 2002-2453433 20020807
EP 1414432 A2 20040506 EP 2002-786354 20020807
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC,
PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK
JP 2005501060 T2 20050113 JP 2003-518446 20020807
US 2004152753 A1 20040805 US 2004-760672 20040121
PRIORITY APPLN. INFO.: US 2001-311715P P 20010810

WO 2002-US24923 W 20020807

OTHER SOURCE(S): MARPAT 138:163603

AB The invention describes methods of use for an organic nitrate compound, or a pharmaceutically acceptable salt thereof, wherein the organic nitrate compound comprises at least one sulfur atom and/or at least one disulfide group. The invention also provides methods for treating, preventing and/or reducing inflammation, pain, and fever; for decreasing or reversing the **gastrointestinal**, renal and other toxicities resulting from the use of nonsteroidal antiinflammatory compds.; for treating and/or preventing **gastrointestinal** disorders; for treating inflammatory disease states and disorders; for treating and/or preventing ophthalmic diseases or disorders; for treating and/or improving the **gastrointestinal** properties of COX-2 inhibitors; for facilitating wound healing; for treating and/or preventing other disorders resulting from elevated levels of cyclooxygenase-2; for decreasing the recurrence of **ulcers**; for improving gastroprotective properties, anti-Helicobacter pylori properties or antacid properties of proton pump inhibitors; for treating Helicobacter pylori and viral infections. For improving gastroprotective properties of H₂ receptor antagonists; for treating and/or preventing inflammations and microbial infections, multiple sclerosis, and viral infections; for treating or preventing restenosis, autoimmune diseases, pathol. conditions resulting from abnormal cell proliferation, polycystic kidney disease, inflammatory diseases or to inhibit wound contraction; for treating or preventing sexual dysfunctions in males and females, for enhancing sexual responses in males and females; for treating or preventing benign prostatic hyperplasia, hypertension, congestive heart failure, variant (Prinzmetal) angina, glaucoma, neurodegenerative disorders, vasospastic diseases, cognitive disorders, urge incontinence, and overactive bladder; for reversing the state of anesthesia. For treating or preventing diseases induced by the increased metabolism of cyclic guanosine 3',5'-monophosphate (cGMP); for treating respiratory disorders and for treating neurol. conditions.

IT 130432-17-6, SPM 3672 139146-65-9

, SPM 5186 139146-66-0, SPM

5185

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL

Searcher : Shears 571-272-2528

10/760672

(Biological study); USES (Uses)

(methods for novel sulfur-containing organic nitrate compds. use in the treatment and prevention of human diseases and conditions)

L5 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2006 ACS on STN

ED Entered STN: 14 Nov 2002

ACCESSION NUMBER: 2002:864914 CAPLUS

DOCUMENT NUMBER: 138:395694

TITLE: NO-donors (VII [1]): synthesis and cyclooxygenase inhibitory properties of N- and S-nitrooxypivaloyl-cysteine derivatives of naproxen - a novel type of NO-NSAID

AUTHOR(S): Kartasasmita, Rahmana E.; Laufer, Stefan; Lehmann, Jochen

CORPORATE SOURCE: Institute of Pharmacy, University of Bonn, Bonn, D-53121, Germany

SOURCE: Archiv der Pharmazie (Weinheim, Germany) (2002), 335(8), 363-366

CODEN: ARPMAS; ISSN: 0365-6233

PUBLISHER: Wiley-VCH Verlag GmbH & Co. KGaA

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Nitric oxide (NO) has been reported to subserve many of the same mucosal protection mechanisms as prostaglandins and is sufficient for acute gastroprotection and **ulcer** healing. In fact, NO-donating NSAID hybrid compds. such as the nitrooxybutyl ester of naproxen show reduced **ulcerogenic** activity while maintaining anti-inflammatory activity. We introduce two prototypes of novel triple-hybrid compds. consisting of cysteine which is known to enhance the activity of organic nitrates and to reduce nitrate tolerance, an NSAID (naproxen), and an organic nitrate (nitrooxypivaloic acid). L-Cysteine Et ester first was N-acylated in a CH₂Cl₂/H₂O two-phase system using the acid chlorides of naproxen or nitrooxypivaloic acid, resp., and sodium acetate, or alternatively using the DCC-activated nitrooxy acid in absolute CH₂Cl₂. The N-acylated intermediates were subsequently S-acylated using the acid chlorides or alternatively the carbonyldiimidazole (CDI)-activated acids again. The two naproxen-cysteine-nitrate hybrid prodrugs were screened in vitro for their cyclooxygenase inhibitory properties relative to naproxen. In this screening the N-nitrooxyacylcysteine derivative was found to be inactive in the concentration range of 0.1-10 µmol/L against both COX-1 and COX-2, while the S-nitrooxyacylcysteine derivative had only weak activity against COX-1.

IT 130432-17-6P

RL: PRP (Properties); RCT (Reactant); SPN (Synthetic preparation);

PREP (Preparation); RACT (Reactant or reagent)

(synthesis and cyclooxygenase inhibitory properties of novel NO-NSAID nitrooxypivaloyl-cysteine derivs. of naproxen)

REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2006 ACS on STN

ED Entered STN: 09 Nov 2000

ACCESSION NUMBER: 2000:785898 CAPLUS

DOCUMENT NUMBER: 133:329627

TITLE: Tetracyclic cGMP-specific phosphodiesterase inhibitors and their use in disease treatment

INVENTOR(S): Daugan, Alain Claude Marie; Gellibert, Françoise

Searcher : Shears 571-272-2528

Anders
AP-3

10/760672

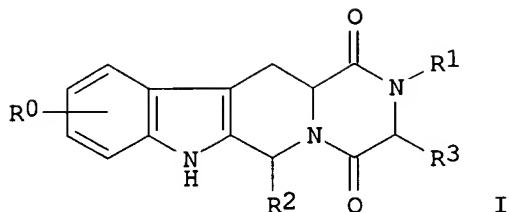
PATENT ASSIGNEE(S): Icos Corp., USA
 SOURCE: U.S., 30 pp., Cont.-in-part of PCT 9519978.
 CODEN: USXXAM
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 4
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
<u>US 6143746</u>	A	20001107	US 1998-154051	19980916
<u>WO 9519978</u>	A1	19950727	WO 1995-EP183	19950119
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US				
RW: KE, MW, SD, SZ, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
WO 9703675	A1	19970206	WO 1996-EP3024	19960711
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA				
WO 9703985	A1	19970206	WO 1996-EP3025	19960711
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG				
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US 6025494	A	20000215	US 1998-133078	19980812
CA 2340636	AA	20000323	CA 1999-2340636	19990826
EP 1113800	A1	20010711	EP 1999-945201	19990826
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002524516	T2	20020806	JP 2000-569812	19990826
<u>US 6127542</u>	A	20001003	US 1999-399667	19990921
<u>US 6369059</u>	B1	20020409	US 2000-633431	20000807
<u>CZ 289832</u>	B6	20020417	CZ 2000-3428	20000919
<u>US 2002119976</u>	A1	20020829	US 2002-68114	20020205
<u>US 6784179</u>	B2	20040831		
<u>JP 2004217674</u>	A2	20040805	JP 2004-125881	20040421
PRIORITY APPLN. INFO.:			GB 1994-1090	A 19940121
			WO 1995-EP183	A2 19950119
			GB 1995-14464	A 19950714
			GB 1995-14465	A 19950714
			WO 1996-EP3024	A2 19960711
			WO 1996-EP3025	A2 19960711
			JP 1995-519339	A3 19950119

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CZ 1998-33	A3 19960711
US 1996-669389	A3 19960716
US 1998-133078	A1 19980812
US 1998-154051	A 19980916
WO 1999-US19466	W 19990826
US 1999-399667	A1 19990921
US 2000-633431	A1 20000807

OTHER SOURCE(S): MARPAT 133:329627
GI



AB A compound of formula I (R0 = H, halogen, C1-6 alkyl; R1 = H, C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, halo-C1-6 alkyl, C3-8 cycloalkyl, C3-8 cycloalkyl-C1-3 alkyl, aryl-C1-3 alkyl, heteroaryl-C1-3 alkyl; R2 = (substituted) monocyclic aromatic ring selected from benzene, thiophene, furan, and pyridine, or (substituted) bicyclic ring (a) attached to the rest of the mol. via one of the benzene ring carbon atoms, and wherein the fused ring is a 5- or 6-membered ring which may be saturated or partially or fully unsatd., and comprises carbon atoms and optionally one or two heteroatoms selected from oxygen, sulfur, and nitrogen; R3 = H, C1-3 alkyl, or R1 and R3 together = 3- or 4-membered alkyl or alkenyl chain) and salts and solvates thereof is disclosed. Compound I is a potent and selective inhibitor of cyclic guanosine 3',5'-monophosphate-specific phosphodiesterase, having a utility in a variety of therapeutic areas where such inhibition is beneficial, including the treatment of cardiovascular disorders and erectile dysfunction. Thus, many I compds. were synthesized and tested in vitro as inhibitors of cGMP phosphodiesterase. Cis-2,3,6,7,12,12a-hexahydro-2-(4-pyridylmethyl)-6-(3,4-methylenedioxyphenyl)pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione showed IC50 of 10 nM.

IT 130432-17-6 *SPM 3672 Form II*
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(drug containing phosphodiesterase inhibitor and; tetracyclic cyclic GMP-specific phosphodiesterase inhibitors and their use in disease treatment)

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

FILE 'MEDLINE' ENTERED AT 14:29:43 ON 17 MAR 2006

Searcher : Shears 571-272-2528

Cl 1
\$
12

Comm
col. 9
1. 35
0

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L6 0 S L5

(FILE 'CAPLUS' ENTERED AT 14:30:07 ON 17 MAR 2006)

L7 9 SEA FILE=CAPLUS ABB=ON PLU=ON (NITRATOPIVAL? OR NITRATO
PIVAL?) (S) ESTER

L8 0 SEA FILE=CAPLUS ABB=ON PLU=ON L7 AND (GASTROINTESTIN? OR
ULCER? OR GASTR? INTESTIN?)

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH,
JICST-EPLUS, JAPIO' ENTERED AT 14:31:13 ON 17 MAR 2006)

L10 56 S L7(S) (ET OR ETHYL)

L11 4 S L10 AND (GASTROINTESTIN? OR ULCER? OR GASTR? INTESTIN?)

L12 4 DUP REM L11 (0 DUPLICATES REMOVED)

L12 ANSWER 1 OF 4 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN

ACCESSION NUMBER: 2000-271365 [23] WPIDS

DOC. NO. CPI: C2000-082857

TITLE: New carboline derivatives, useful for treatment of
e.g. erectile dysfunction, angina, hypertension,
congestive heart failure, stroke, ulcers
and dysmenorrhea, are cGMP (cyclic guanosine
monophosphate)-specific phosphodiesterase inhibitors.

DERWENT CLASS: B02 C02

INVENTOR(S): BOMBRUN, A; GELLIBERT, F

PATENT ASSIGNEE(S): (ICOS-N) ICOS CORP; (BOMB-I) BOMBRUN A

COUNTRY COUNT: 83

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000015639	A1	20000323	(200023)*	EN	86
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW					
NL OA PT SD SE SZ UG ZW					
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB					
GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV					
MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR					
TT UA UG US UZ VN YU ZW					
AU 9910258	A	20000403	(200034)		

Searcher : Shears 571-272-2528

10/760672

BR 9816018 A 20010605 (200138)
 EP 1114048 A1 20010711 (200140) EN
 R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
 JP 2002524564 W 20020806 (200266) 75
 US 6462047 B1 20021008 (200269)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000015639	A1	WO 1998-EP6050	19980916
AU 9910258	A	WO 1998-EP6050	19980916
		AU 1999-10258	19980916
BR 9816018	A	BR 1998-16018	19980916
		WO 1998-EP6050	19980916
EP 1114048	A1	EP 1998-952629	19980916
		WO 1998-EP6050	19980916
JP 2002524564	W	WO 1998-EP6050	19980916
		JP 2000-570177	19980916
US 6462047	B1	WO 1998-EP6050	19980916
		US 2001-744859	20010516

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 9910258	A Based on	WO 2000015639
BR 9816018	A Based on	WO 2000015639
EP 1114048	A1 Based on	WO 2000015639
JP 2002524564	W Based on	WO 2000015639
US 6462047	B1 Based on	WO 2000015639

PRIORITY APPLN. INFO: WO 1998-EP6050 19980916

AN 2000-271365 [23] WPIDS

AB WO 200015639 A UPAB: 20000516

NOVELTY - Carboline derivatives (I), their salts and solvates, are new.

DETAILED DESCRIPTION - Carboline derivatives of formula (I), their salts and solvates, are new.

A = 5 - 6 membered heteroaryl group containing at least 1 heteroatom selected from O, N and S;

R0 = H or halogen;

R1 = H, nitro, trifluoromethyl, trifluoromethoxy, halogen, cyano, 5 - 6 membered heteroaryl group containing at least 1 heteroatom selected from O, N and S, (optionally substituted by C(O)ORa or 1-4C alkyl), 1-6C alkyl optionally substituted by ORa, 1-3C alkoxy, C(O)Ra, OC(O)Ra, C(O)Ra, (1-4C alkylene)-Het, (1-4C alkylene)-C(O)ORa, O-(1-4C alkylene)-C(O)ORa, (1-4C alkylene)-O-(1-4C alkylene)-C(O)ORa, C(O)NRaSO2Rc, C(O)-(1-4C alkylene)-Het, (1-4C alkylene)-NRaRb, (2-6C alkylene)-NRaRb, C(O)NRaRb, C(O)RaRc, C(O)NRa-(1-4C alkylene)-ORb, C(O)NRa-(1-4C alkylene)-Het, ORa, O-(2-4C alkylene)-NRaRb, O-(1-4C alkylene)-Het, O-(2-4C alkylene)-ORa, O-(2-4C alkylene)-NRaC(O)ORb, NRaRb, NRa-(1-4C alkylene)-NRaRb, NRaC(O)Rb, NRaC(O)NRaRb, N(SO2-(1-4C alkyl))2, NRa(SO2-(1-4C alkyl), SO2NRaRb or OSO2CF3;

R2 = H, halogen, ORa, 1-6C alkyl, nitro or NRaRb; or

R1 + R2 = 3 or 4 membered alkylene or alkenylene chain, optionally containing at least 1 heteroatom component of a 5 or 6 membered ring;

R3 = H, halogen, NO2, trifluoromethoxy, 1-6C alkyl, O-(1-6C

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alkyl), or C(O)ORa;

R4 = H; or

R3 + R4 = 3 or 4 membered alkylene or alkenylene chain component of a 5 or 6 membered ring, optionally containing at least 1 heteroatom;

Het = 5 or 6 membered heterocyclic group containing at least 1 O, N and/or S, and is optionally substituted by 1-4C alkyl;

Ra, Rb = H or 1-6C alkyl;

Rc = phenyl or 4-6C cycloalkyl, both optionally substituted by 1 or more halogen, C(O)ORa or ORa;

n = 1 - 3; and

m = 1 or 2.

INDEPENDENT CLAIMS are provided for:

(1) a composition comprising (I) and a second active agent for simultaneous, separate or sequential use; and

(2) a process for the preparation of (I).

ACTIVITY - Vasotropic; centrally active; endocrine; antianginal; hypotensive; respiratory; cytostatic; cardiant; nephrotropic; antiarteriosclerotic; antiaggregant; hemostatic; antiinflammatory; cerebroprotective; antiasthmatic; ophthalmological; antiulcer; gastrointestinal; osteopathic; tocolytic; gynecological; analgesic (all claimed)

MECHANISM OF ACTION - Phosphodiesterase V inhibitor; acetylcholine esterase inhibitor; neutral endopeptidase inhibitor; adrenergic antagonist.

(I) were administered to spontaneously hypertensive rats at 5 mg/kg in 5% DMF and 95% olive oil. Blood pressure was measured using a catheter in the carotid artery and recorded for 5 hours post administration. The area under curve for (E)-1R-1-(1-(2,3-dihydrobenzofuran-5-yl)-2,3,4,9-tetrahydro- beta -carbolin-2-yl)-3-(pyrrolidin-1-yl)-propen-1-one (Ia) was 9 mm Hg/hour.

USE - As cGMP (cyclic guanosine monophosphate)-specific phosphodiesterase inhibitors for treatment of erectile dysfunction, angina, hypertension, pulmonary or malignant hypertension, COPD (chronic obstructive pulmonary disease), pheochromocytoma, ARDS (not defined), congestive heart failure, renal failure, atherosclerosis, reduced blood vessel patency, peripheral vascular disease, vascular disorder, thrombocytopenia, inflammatory disease, myocardial infarction, stroke, bronchitis, asthma, allergic rhinitis, glaucoma, peptic ulcer, gut motility disorder, post-percutaneous transluminal coronary angioplasty, carotid angioplasty, post-surgical graft stenosis, osteoporosis, pre-term labor, benign prostatic hypertrophy, female sexual dysfunction, dysmenorrhea and IBS (irritable bowel syndrome) (claimed).

ADVANTAGE - Good oral bioavailability, specific for phosphodiesterase 5.
Dwg. 0/0

L12 ANSWER 2 OF 4 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2000-271237 [23] WPIDS
CROSS REFERENCE: 1995-275237 [36]; 1997-132562 [12]; 2001-023419 [03]
DOC. NO. CPI: C2000-082747
TITLE: Composition for simultaneous, separate, or sequential use in the treatment of e.g. erectile dysfunction, comprises a tetracyclic phosphodiesterase inhibitor and a second active agent, e.g. vasodilator, acetylcholine esterase inhibitor.
DERWENT CLASS: B05
INVENTOR(S): DAUGAN, A C; GELLIBERT, F

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1/4

10/760672

PATENT ASSIGNEE(S): (ICOS-N) ICOS CORP
COUNTRY COUNT: 87
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000015228	A1	20000323	(200023)*	EN	89
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW					
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZA ZW					
AU 9957856	A	20000403	(200034)		
BR 9913824	A	20010619	(200140)		
EP 1113800	A1	20010711	(200140)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI					
JP 2002524516	W	20020806	(200266)		84

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000015228	A1	WO 1999-US19466	19990826
AU 9957856	A	AU 1999-57856	19990826
BR 9913824	A	BR 1999-13824	19990826
		WO 1999-US19466	19990826
EP 1113800	A1	EP 1999-945201	19990826
		WO 1999-US19466	19990826
JP 2002524516	W	WO 1999-US19466	19990826
		JP 2000-569812	19990826

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 9957856	A Based on	WO 2000015228
BR 9913824	A Based on	WO 2000015228
EP 1113800	A1 Based on	WO 2000015228
JP 2002524516	W Based on	WO 2000015228

PRIORITY APPLN. INFO: US 1998-154051 19980916
AN 2000-271237 [23] WPIDS
CR 1995-275237 [36]; 1997-132562 [12]; 2001-023419 [03]
AB WO 200015228 A UPAB: 20021014

NOVELTY - A composition for the simultaneous, separate or sequential use in the treatment of a condition by inhibition of a cGMP specific phosphodiesterase, comprises a tetracyclic compound (I) and a second therapeutically active agent.

DETAILED DESCRIPTION - A composition for the simultaneous, separate or sequential use in the treatment of a condition by inhibition of a cGMP specific phosphodiesterase, comprises a tetracyclic compound of formula (I), and salts and solvates, and a second therapeutically active agent.

R0 = H, halogen or 1-6C alkyl;

R1 = H, 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, halo-(1-6C)-alkyl, 3-8C cycloalkyl, 3-8C cycloalkyl-(1-3C)-alkyl, aryl-(1-3C)-alkyl or heteroaryl-(1-3C)-alkyl;

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R2 = optionally substituted monocyclic aromatic ring selected from benzene, thiophene, furan, pyridine or an optionally substituted bicyclic ring of formula (i), attached to the rest of the molecule via one of the benzene C atoms;

A = 5 - 6 membered ring optionally containing 1 - 2 O, S and or N; and

R3 = H or 1-3C alkyl; or

R1 + R2 = 3-4C alkyl or 3-4C alkenyl.

ACTIVITY - Vasodilator; antianginal; hypotensive; respiratory; antiatherosclerotic; cardiant; vasotropic; hemostatic; antiinflammatory; cerebroprotective; antiasthmatic; antiallergic; ophthalmological; antiulcer; cytostatic; gastrointestinal, CNS active; endocrine.

MECHANISM OF ACTION - Phosphodiesterase inhibitor.

cGMP-PDE (cyclic GMP dependent phosphodiesterase) activity was measured using a one-step assay adapted from Wells et al., Biochim. Biophys. Acta, 384, 430 (1975). The reaction medium contained 50 mM Tris-HCl, pH 7.5, 5 mM magnesium acetate, 250 micro g/ml 5'-nucleotidase, 1 mM EGTA (ethylenedis(oxyethylenenitrolo)tetraacetic acid and 0.15 micro M 8-(H3)-cGMP. The enzyme used was human recombinant PDE-5. (I) were dissolved in DMSO (dimethylsulfoxide) finally present at 2 % in the assay. The incubation time was 30 minutes during which the total substrate conversion did not exceed 30 %. Cis-2,3,6,7,12,12a-hexahydro-6-(2,3-dihydrobenzo(b)-furan-5-yl)-2-methylpyrazine(2',1':6,1)pyrido(3,4-b)indole-1,4-dione (Ia) had an IC50 of less than 10 nM.

USE - The composition is used to treat stable angina, unstable angina, variant angina, hypertension, pulmonary hypertension, chronic obstructive pulmonary disease, malignant hypertension, pheochromocytoma, congestive heart failure, acute respiratory distress syndrome, acute renal failure, chronic renal failure, atherosclerosis, a condition of reduced blood vessel patency, postpercutaneous transluminal coronary angioplasty, carotid angioplasty, myocardial infarction, post-bypass surgery graft stenosis, a peripheral vascular disease, a vascular disorder, Raynaud's disease, thrombocythemia, an inflammatory disease, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma, peptic ulcer, osteoporosis, preterm labor, benign prostatic hypertrophy, a gut motility disorder, irritable bowel syndrome or male or female mammalian erectile dysfunction, preferably erectile dysfunction, especially human erectile dysfunction (claimed).

Dwg.0/0

L12 ANSWER 3 OF 4 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN
 ACCESSION NUMBER: 2001-023419 [03] WPIDS
 CROSS REFERENCE: 1995-275237 [36]; 1997-132562 [12]; 2000-271237 [23]
 DOC. NO. CPI: C2001-007100
 TITLE: Use of hexahydro-pyrazino-pyrido-indole-dione derivative and another drug for treatment of conditions benefiting from cGMP-specific phosphodiesterase inhibition e.g. erectile dysfunction.
 DERWENT CLASS: B05 C03
 INVENTOR(S): DAUGAN, A C; GELLIBERT, F
 PATENT ASSIGNEE(S): (ICOS-N) ICOS CORP
 COUNTRY COUNT: 1
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
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Searcher	:	Shears	571-272-2528
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 US 6143746 A 20001107 (200103)* 30

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 6143746	A CIP of	WO 1995-EP183 US 1998-154051	19950119 19980916

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PRIORITY APPLN. INFO: GB 1995-14474 19950714; GB
 1994-1090 19940121; GB
 1995-14465 19950714

AN 2001-023419 [03] WPIDS
 CR 1995-275237 [36]; 1997-132562 [12]; 2000-271237 [23]
 AB US 6143746 A UPAB: 20010116

NOVELTY - A combination of a 2,3,6,7,12,12a-hexahydro-pyrazino(2',1';6,1)pyrido(3,4-b)indole-1,4-dione derivative (I) and another drug (II) is claimed for simultaneous, separate or sequential use in the treatment of conditions where inhibition of cGMP-specific phosphodiesterase (PDE) is of therapeutic benefit.

DETAILED DESCRIPTION - A combination of a 2,3,6,7,12,12a-hexahydro-pyrazino(2',1';6,1)pyrido(3,4-b)indole-1,4-dione of formula (I) and another drug (II) is claimed for simultaneous, separate or sequential use in the treatment of conditions where inhibition of cGMP-specific phosphodiesterase (PDE) is of therapeutic benefit.

R0 = H, halogen or 1-4C alkyl;

R1 = H, 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, 1-6C haloalkyl, 3-8C cycloalkyl, (3-8C)cycloalkyl(1-3C)alkyl, aryl(1-3C)alkyl or heteroaryl(1-3C)alkyl;

R2 = phenyl, thienyl, furyl or pyridyl, where phenyl is optionally fused to a 5- or 6-membered ring containing 0-2 heteroatoms selected from O, S and N; and

R3 = H or 1-3C alkyl; or

R1+R3 = 3-4C alkylene or alkenylene.

ACTIVITY - Vasotropic; antianginal; hypotensive; cardiant; nephrotropic; antiarteriosclerotic; vasotropic; antiinflammatory; cerebroprotective; antiasthmatic; antiallergic; ophthalmological; antiulcer; osteopathic; laxative; antidiarrheic.

MECHANISM OF ACTION - Phosphodiesterase-5 inhibitor.

The hypotensive effects of (I) and (II) were studied in conscious spontaneously hypertensive rats. Various mixtures of (I) and (II) gave results expressed as Area Under Curve (AUC) from 0-5 hours in mmHg.hours, of the fall in blood pressure over time of 77-171.

USE - The combination is especially useful for treating conditions where inhibition of PDE5 is of therapeutic benefit, in humans or nonhuman animals, especially erectile dysfunction, stable angina, unstable angina, variant angina, hypertension, pulmonary hypertension, chronic obstructive pulmonary disease, acute respiratory distress syndrome, malignant hypertension, pheochromocytoma, congestive heart failure, acute renal failure, chronic renal failure, atherosclerosis, a condition of reduced blood vessel patency, peripheral vascular disease, a vascular disorder, thrombocythemia, inflammatory disease, myocardial infarction, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma, peptic ulcer, gut motility disorders, post-percutaneous transluminal coronary or carotid angioplasty, post-bypass surgery graft stenosis, osteoporosis, preterm labor, benign prostatic hypertrophy or irritable

bowel syndrome.
Dwg.0/0

L12 ANSWER 4 OF 4 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN
 ACCESSION NUMBER: 2000-282560 [24] WPIDS
 CROSS REFERENCE: 1998-076777 [07]
 DOC. NO. CPI: C2000-085192
 TITLE: Combinations comprising carboline derivatives and
 second therapeutic agent for simultaneous, separate
 or sequential treatment of conditions where
 inhibition of cGMP-specific PDE is of therapeutic
 benefit.
 DERWENT CLASS: B02
 INVENTOR(S): BOMBRUN, A
 PATENT ASSIGNEE(S): (ICOS-N) ICOS CORP
 COUNTRY COUNT: 1
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 6043252	A	20000328	(200024)*		40

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 6043252	A	CIP of	
		WO 1997-EP2277	19970505
		US 1998-154052	19980916

PRIORITY APPLN. INFO: US 1998-154052 19980916; WO
 1997-EP2277 19970505

AN 2000-282560 [24] WPIDS
 CR 1998-076777 [07]
 AB US 6043252 A UPAB: 20000522

NOVELTY - Combinations comprising:

(a) carboline derivatives and their salts and solvates; and
 (b) second therapeutically active agent, for simultaneous,
 separate or sequential use in the treatment of conditions where
 inhibition of a cyclic-guanylic acid (cGMP)-specific phosphodiesterase
 (PDE) is of therapeutic benefit.

DETAILED DESCRIPTION - Carboline derivatives in the combination
 are of formula (I):

R0 = H or halo;

R1 = H, nitro, trifluoromethyl, trifluoromethoxy, halo, cyano,
 5-6-membered heterocyclic group containing at least one heteroatom
 chosen from O, S and N optionally substituted by C(=O)ORa or 1-4C
 alkyl, 1-6C alkyl optionally substituted by ORa, 1-3C alkoxy, C(=O)Ra,
 OC(=O)Ra, C(=O)ORa, 1-4C alkylene-C(=O)ORa, O-(1-4C)
 alkylene-C(=O)ORa, 1-4C alkylene-O-(1-4C) alkylene-C(=O)ORa,
 C(=O)NRaSO2Rc, C(=O)-(1-4C) alkylene-Het, 1-4C alkylene-NRaRb, 2-6C
 alkenylene-NRaRb, C(=O)NRaRb, C(=O)NRaRc, C(=O)NRa-(1-4C)
 alkylene-ORb, C(=O)NRa-(1-4C) alkylene-Het, ORa O-(2-4C)
 alkylene-NRaRb, O-(1-4C) alkylene-CH(ORa) CH2NRaRb, O-(1-4C)
 alkylene-Het, O-(2-4C) alkylene-ORa, O-(2-4C) alkylene-NRa-C(=O)ORb,
 NRaRb, NRa-(1-4C) alkylene-NRaRb, NRaC(=O)Rb, NRaC(=O)NRaRb,
 N-(SO2-(1-4C) alkyl)2, NRa(SO2-1(1-4C) alkyl), SO2NRaRb or
 OSO2-trifluoromethyl;

R2 = H, halo, ORa, 1-6C alkyl, NO2, NRaRb; or

*Same
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1/2 of 4*

R1+R2 = 3-4-membered alkylene or alkenylene chain component of a 5-6-membered ring optionally containing at least one heteroatom chosen from O, S or N;

R3 = H, halo, nitro, trifluoromethoxy, 1-6C alkyl or C(=O)ORa;

R4 = H; or

R3+R4 = 3-4-membered alkylene or alkenylene chain component of a 5-6-membered ring optionally containing at least one heteroatom;

Het = 5-6-membered heterocyclic ring containing at least one heteroatom chosen from O, S or N and optionally substituted by 1-4C alkyl;

Ra, Rb = H or 1-6C alkyl;

Rc = phenyl or 4-6C cycloalkyl optionally substituted by one or more of halo, one or more of C(=O)ORa or one or more of ORa;

n = 1-3; and

m = 1-2.

ACTIVITY - Antianginal, Hypotensive; Cardiant; Antiarteriosclerotic; Antiinflammatory; Cerebroprotective; Antiasthmatic; Antiallergic; Antiulcer; Osteopathic; Cytostatic; Vasotropic.

The hypotensive effects of 17 test compounds (I) were examined in conscious spontaneously hypertensive rats (SHR). The compounds were administered at doses of 5 mg/kg in a mixture of 5% dimethylformamide and 95% olive oil. Blood pressure was measured from a catheter inserted in the carotid artery and recorded for 5 hours after administration. The results were expressed as area-under-the-curve (AUC 0-5) (mmHg/hour) of the fall in blood pressure over time. The results ranged from 52-128 mmHg/hour.

MECHANISM OF ACTION - cGMP-specific PDE inhibitor; vasodilator; alpha -adrenergic blocker; mixed alpha , beta -blocker; alpha 2-adrenergic blocker; ACE inhibitor; NEP inhibitor; centrally acting dopaminergic agent; calcium channel blocker; diuretic.

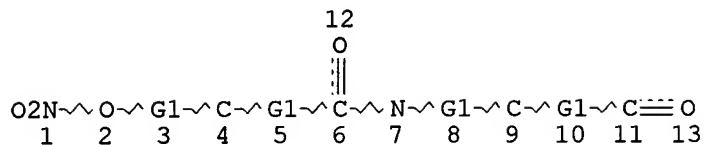
Test compounds (I) were tested for cGMP-PDE activity using a one-step assay Wells et al. Biochim Biophys Acta 1975; 384: 430 and human recombinant PDE5. The test compounds were dissolved in dimethylsulfoxide finally present at 2% in the assay. The incubation period was 30 minutes, during which the total substrate conversion did not exceed 30%. The IC50 values were determined and ranged from 2-72 nM.

USE - The combinations are used for simultaneous, separate or sequential treatment of conditions where inhibition of cGMP-specific PDE is of therapeutic benefit including stable angina, unstable angina, variant angina, hypertension, pulmonary hypertension, chronic obstructive pulmonary disease, malignant hypertension, pheochromocytoma, congestive heart failure, acute respiratory distress syndrome, acute renal failure, chronic renal failure, atherosclerosis, conditions of reduced blood vessel patency, post-percutaneous transluminal coronary angioplasty, carotid angioplasty, myocardial infarction, post-bypass surgery graft stenosis, peripheral vascular disease, vascular disorders, Raynaud's disease, thrombocythemia, inflammatory disease, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma, peptic ulcer, osteoporosis, pre-term labor, benign prostatic hypertrophy, gut motility disorder or irritable bowel syndrome, or erectile dysfunction in male or female animals (claimed).
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FILE 'HOME' ENTERED AT 14:32:20 ON 17 MAR 2006

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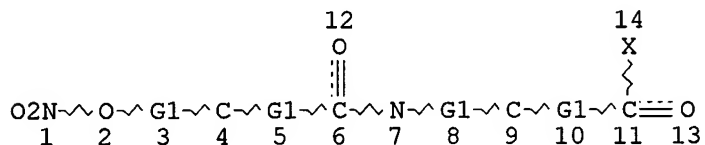
=> d que stat l4; d his ful
L1 STR



REP G1=(0-10) CH2
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 13

STEREO ATTRIBUTES: NONE
L2 113 SEA FILE=REGISTRY SSS FUL L1
L3 STR



REP G1=(0-10) CH2
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 14

STEREO ATTRIBUTES: NONE
L4 0 SEA FILE=REGISTRY SUB=L2 SSS FUL L3

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L1 STR
L2 113 SEA SSS FUL L1

L3 STR L1
L4 0 SEA SUB=L2 SSS FUL L3

FILE 'REGISTRY' ENTERED AT 16:55:36 ON 16 MAR 2006
D QUE STAT

FILE 'CAPLUS' ENTERED AT 16:55:44 ON 16 MAR 2006

Searcher : Shears 571-272-2528

10/760672

L5 46 SEA ABB=ON PLU=ON L2
L6 4 SEA ABB=ON PLU=ON L5 AND (ULCER? OR GASTROINTESTIN? OR
GASTR? INTESTIN?)
SEL HIT L6 1-4 RN
DEL SEL Y
L7 0 SEA ABB=ON PLU=ON L6 NOT (PY=>2001 OR PD=>20010810)

FILE 'HOME' ENTERED AT 17:08:13 ON 16 MAR 2006
D QUE STAT L4

FILE REGISTRY

Property values tagged with IC are from the ZIC/VINITI data file
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STRUCTURE FILE UPDATES: 15 MAR 2006 HIGHEST RN 877033-93-7
DICTIONARY FILE UPDATES: 15 MAR 2006 HIGHEST RN 877033-93-7

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*
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added, *
* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *
*

Structure search iteration limits have been increased. See HELP SLIMI
for details.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document. For information
on property searching in REGISTRY, refer to:

<http://www.cas.org/ONLINE/UG/regprops.html>

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FILE LAST UPDATED: 15 Mar 2006 (20060315/ED)

Searcher : Shears 571-272-2528

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(FILE 'HOME' ENTERED AT 14:21:51 ON 17 MAR 2006)
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FILE 'REGISTRY' ENTERED AT 14:21:56 ON 17 MAR 2006

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L1 2 SEA ABB=ON PLU=ON ("SPM 5185"/CN OR "SPM 5186"/CN)
D CN
D CN 2
E "SP/W 4757"/CN 5
L2 2 SEA ABB=ON PLU=ON "SP/W 3672"/CN OR "SP/W 6373"/CN
L3 4 SEA ABB=ON PLU=ON L1 OR L2

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D L3 1-4 IDE

FILE 'CAPLUS' ENTERED AT 14:24:11 ON 17 MAR 2006

L*** DEL 31 S SPM4757 OR SPM5186 OR SPM5185 OR SPM3672 OR SPM6373 OR (S
L*** DEL 1 S L4 AND (GASTROINTESTIN? OR ULCER? OR GASTR? INTESTIN?)
L*** DEL 0 S SPW4757
L*** DEL 3 S SPW5186
D KWIC
L*** DEL 31 S SPM4757 OR SPM5186 OR SPM5185 OR SPM3672 OR SPM6373 OR SP
L*** DEL 1 S L4 AND (GASTROINTESTIN? OR ULCER? OR GASTR? INTESTIN?)
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FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH,
JICST-EPLUS, JAPIO' ENTERED AT 14:27:26 ON 17 MAR 2006

L*** DEL 0 S L5

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SPM3672 OR SPM6373 OR SPW4757 OR SPW5186 OR SPW3672 OR
SPW6373 OR (SPM OR SP(W)W OR SPW) (W) (4757 OR 5186 OR 5185
OR 3672 OR 6373)
L5 3 SEA ABB=ON PLU=ON L4 AND (GASTROINTESTIN? OR ULCER? OR
GASTR? INTESTIN?)
D QUE
D 1-3 .BEVSTR

FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH,
JICST-EPLUS, JAPIO' ENTERED AT 14:29:43 ON 17 MAR 2006

L6 0 SEA ABB=ON PLU=ON L5

FILE 'CAPLUS' ENTERED AT 14:30:07 ON 17 MAR 2006

L7 9 SEA ABB=ON PLU=ON (NITRATOPIVAL? OR NITRATO PIVAL?) (S) EST
ER
L8 0 SEA ABB=ON PLU=ON L7 AND (GASTROINTESTIN? OR ULCER? OR
GASTR? INTESTIN?)
D QUE

FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH,
JICST-EPLUS, JAPIO' ENTERED AT 14:31:13 ON 17 MAR 2006

L9 59 SEA ABB=ON PLU=ON L7
L10 56 SEA ABB=ON PLU=ON L7(S) (ET OR ETHYL)
L11 4 SEA ABB=ON PLU=ON L10 AND (GASTROINTESTIN? OR ULCER? OR
GASTR? INTESTIN?)

Searcher : Shears 571-272-2528

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L12 4 DUP REM L11 (0 DUPLICATES REMOVED)
D 1-4 IBIB ABS

FILE 'HOME' ENTERED AT 14:32:20 ON 17 MAR 2006
D COST
D QUE L3

FILE 'REGISTRY' ENTERED AT 14:36:13 ON 17 MAR 2006
E "SP/W 4757"/CN 5
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E SPM 4757/CN 5
E "SPM-4757"/CN 5

FILE HOME

FILE REGISTRY

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DICTIONARY FILE UPDATES: 15 MAR 2006 HIGHEST RN 877033-93-7

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Please note that search-term pricing does apply when conducting SmartSELECT searches.

*
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added, *
* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *
*

Structure search iteration limits have been increased. See HELP SLIMI for details.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

<http://www.cas.org/ONLINE/UG/regprops.html>

FILE CAPLUS

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strictly prohibited.

FILE COVERS 1907 - 17 Mar 2006 VOL 144 ISS 13
FILE LAST UPDATED: 16 Mar 2006 (20060316/ED)

Effective October 17, 2005, revised CAS Information Use Policies apply
They are available for your review at:

<http://www.cas.org/infopolicy.html>

FILE MEDLINE

FILE LAST UPDATED: 16 MAR 2006 (20060316/UP). FILE COVERS 1950 TO DA

On December 11, 2005, the 2006 MeSH terms were loaded.

The MEDLINE reload for 2006 is now (26 Feb.) available. For details
on the 2006 reload, enter HELP RLOAD at an arrow prompt (=>).
See also:

<http://www.nlm.nih.gov/mesh/>
http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html
http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_med_data_changes.ht
http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_2006_MeSH.html

OLDMEDLINE is covered back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
MeSH 2006 vocabulary.

This file contains CAS Registry Numbers for easy and accurate
substance identification.

FILE BIOSIS

FILE COVERS 1969 TO DATE.

CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 15 March 2006 (20060315/ED)

FILE EMBASE

FILE COVERS 1974 TO 17 Mar 2006 (20060317/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

The updates on February 20 and 24, 2006, were incomplete due to a
technical problem. The problem has been corrected, and the missing
records were included in the update on March 3, 2006. If you
received SDI results from the original updates on February 20 and 24,
you will automatically be credited for the update that was rerun on
March 3.

If you have any questions, please contact your STN Service Center.

This file contains CAS Registry Numbers for easy and accurate
substance identification.

FILE WPIDS

FILE LAST UPDATED: 15 MAR 2006 <20060315/UP>

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MOST RECENT DERWENT UPDATE: 200618 <200618/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE,
PLEASE VISIT:
http://www.stn-international.de/training_center/patents/stn_guide.pdf

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES, SEE
<http://scientific.thomson.com/support/patents/coverage/latestupdates/>

>>> FOR INFORMATION ON ALL DERWENT WORLD PATENTS INDEX USER
GUIDES, PLEASE VISIT:
<http://scientific.thomson.com/support/products/dwpi/>

>>> FAST-ALERTING ACCESS TO NEWLY-PUBLISHED PATENT
DOCUMENTATION NOW AVAILABLE IN DERWENT WORLD PATENTS INDEX
FIRST VIEW - FILE WPIFV.
FOR FURTHER DETAILS:
<http://scientific.thomson.com/support/products/dwpifv/>

>>> THE CPI AND EPI MANUAL CODES WILL BE REVISED FROM UPDATE 200601.
PLEASE CHECK:
<http://scientific.thomson.com/support/patents/dwpieref/reftools/classif>

>>> PLEASE BE AWARE OF THE NEW IPC REFORM IN 2006, SEE
http://www.stn-international.de/stndatabases/details/ipc_reform.html
<http://scientific.thomson.com/media/scpdf/ipcrdwpf.pdf> <<<

FILE CONFSCI
FILE COVERS 1973 TO 25 May 2005 (20050525/ED)

CSA has suspended updates until further notice.

FILE SCISEARCH

FILE COVERS 1974 TO 16 Mar 2006 (20060316/ED)

SCISEARCH has been reloaded, see HELP RLOAD for details.

FILE JICST-EPLUS
FILE COVERS 1985 TO 13 MAR 2006 (20060313/ED)

THE JICST-EPLUS FILE HAS BEEN RELOADED TO REFLECT THE 1999 CONTROLLED
TERM (/CT) THESAURUS RELOAD.

FILE JAPIO
FILE COVERS APR 1973 TO OCTOBER 27, 2005

>>> GRAPHIC IMAGES AVAILABLE <<<

>>> NEW IPC8 DATA AND FUNCTIONALITY NOT YET AVAILABLE IN THIS FILE.
USE IPC7 FORMAT FOR SEARCHING THE IPC. WATCH THIS SPACE FOR FURTHER
DEVELOPMENTS AND SEE OUR NEWS SECTION FOR FURTHER INFORMATION
ABOUT THE IPC REFORM <<<